Express Mail Label No.: EV392162416US
Date of Deposit: June 3, 2004 **Attorney Docket No. 22596-531**

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANT(S):	Jiang *et al.*		
SERIAL NO.:	09/975,776	EXAMINER:	Frederick F. Krass
FILING DATE:	October 10, 2001	ART UNIT:	1614
FOR:	PHARMACEUTICAL COMPOSITIONS CONTAINING β-LAPACHONE, OR DERIVATIVES OR ANALOGS THEREOF, AND METHODS OF USING SAME		

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION OF DR. DASHARATHA REDDY UNDER 37 C.F.R. §1.132

I, DASHARATHA REDDY, of 11C Railroad Street, Acton, MA, declare and state that:

1. I am a co-inventor, together with Zhiwei Jiang, of the subject matter claimed in the above-referenced U.S. patent application.

2. I received my M.S. degree in Chemistry from Kakatiya University, Warangal, India in 1983 and my Ph.D. degree in Organic Chemistry from Indian Institute of Science, Bangalore, India in 1988. I worked as a post-doctoral fellow at Northwestern University, Evanston, Illinois.

3. I am presently employed by ArQule, Inc. (formerly Cyclis Pharmaceuticals, Inc.), 19 Presidential Way, Woburn, Massachusetts, the assignee of the above-referenced patent application. I have been employed by ArQule, Inc. for 3 years. Since the beginning of my career, I have developed novel compositions and methods of preparing solubilizing formulations for different anti-cancer drugs including, β-lapachone and its analogs and derivatives. I have more than 25 publications in the field of anti-cancer drug chemistry.

4. I have reviewed the Office Action dated March 1, 2004. I understand that claims 1,

2, 6, 9, 11, 12, 15, 18, 19, 21, 22, 25, 28, 30-34, 36, 37, 40, 43, 45-48, 51, 54, 180, 182-186 and 204-209 have been rejected under 35 U.S.C. §103(a) as being unpatentable over WO 00/61142 to Pardee ("Pardee"), taken in view of U.S. Patent No. 4,983,586 to Bodor ("Bodor").

5. I have reviewed the present application in conjunction with the Pardee and Bodor references.

6. I make this declaration to rebut the Examiner's assertion, with which I do not agree. It is my opinion that the pending claims are not obvious in view of the combination of Pardee and Bodor. The Examiner asserts that it would have been obvious to have solubilized the anti-neoplastic/anti-tumor agents of the primary reference (β-lapachone and taxol) by complexing them with hydroxypropyl-beta-cyclodextrin of the secondary reference to improve solubility for parenteral administration. To the contrary, one of ordinary skill in the art would not be motivated to combine Pardee and Bodor nor would one of ordinary skill in the art have a reasonable expectation of success combining the teachings of Pardee and Bodor to reach the presently claimed invention.

7. The present invention as claimed is directed to pharmaceutical compostions, formulations and kits comprising a therapeutically effective amount of β-lapachone or analogs and derivatives thereof and the solubilizing carrier molecule beta-cyclodextrin or hydroxypropyl-beta-cyclodextrin. There is no suggestion or motivation to combine Pardee and Bodor to reach the present invention. The ordinary skilled artisan reading Pardee would not be motivated to improve on the solubility of the disclosed anti-cancer agents, β-lapachone or taxol. As stated by the Examiner, Pardee is directed to the combination of these agents in treating cancer in a synergistic manner. In fact, in teaching the combination of these agents to treat cancer, Pardee discloses that the inventors have been successful in solubilizing the water-insoluble β-lapachone compound and the partially water soluble taxol compound using the formulating agent, lipiodol (*See*, page 21, lines 8-10 and lines 16-18) and that these lipiodol formulated compounds of β-lapachone and taxol can

be administered intraperitoneally or intravenously. *See*, page 21, lines 20-21. Specifically, Pardee teaches "β-lapachone was formulated into solution using lipiodol, a medium agent used clinically. **Our success with this formulating agent (lipiodol) solved the long standing problem of insolubility of β-lapachone.**" **(Emphasis Added)**. *See*, page 21, lines 8-10. Pardee also teaches an alternative formulation for solubilizing β-lapachone in cremphor plus ethanol. *See*, page 21, lines 12-14. Further, the working examples of Pardee teach the successful use of β-lapachone and taxol formulated in lipiodol to treat cancer (inhibition of tumor growth, lessening tumors, reducing tumor angiogenesis, *etc.*) *in vivo* by administering these β-lapachone/lipiodol and taxol/lipiodol formulations to mice. *See* page 21, line 7 – page 24, line 8; Figures 2-7. Pardee teaches the formulations showed no toxicity. *See*, page 22, line 14 and line 33.

Since Pardee teaches the solubilization of β-lapachone and taxol in lipiodol and the utility of these formulations in treating cancer without toxic side-effects, the skilled artisan reading Pardee would have no desire or incentive to make a modification to arrive at the claimed invention (*i.e.* a pharmaceutical composition comprising a therapeutically effective amount of β-lapachone solubilized by beta-cyclodextrin or hydroxypropyl-beta-cyclodextrin). The mere fact Pardee could be modified (*i.e.* that β-lapachone or taxol could be solublized by different solubilizing agents/carriers) does not make the modification obvious. Thus, one of ordinary skill in the art reading Pardee would not be motivated to combine the teachings of Pardee with the teachings of Bodor to reach the present invention.

8. Further, one of ordinary skill in the art would not reasonably expect the β-lapachone or analogs or derivatives or taxol compounds disclosed in Pardee to be successfully combined with the general beta-cyclodextrin or hydroxypropyl-beta-cyclodextrin disclosure of Bodor to produce a water-soluble pharmaceutical composition comprising β-lapachone that is therapeutically effective. Bodor does not disclose the use of beta-cyclodextrin for solubilizing β-lapachone or any other compounds but rather Bodor merely discloses the contemplated use of a modified beta-cyclodextrin, hydroxypropyl-beta-cyclodextrin, to solubilize a very broad family of lipophilic or water-insoluble drugs/compounds and a broad genus of anti-neoplastics (anti-

cancer/anti-tumor agents). *See*, Col. 14, line 51 – Col. 15, line 47. In fact, Bodor teaches away from the use of beta-cyclodextrin as a solubilizing agent for water-insoluble or water-poorly soluble drugs/compounds (*i.e.* β-lapachone, taxol, *etc.*) based on the lack of solubility of beta-cyclodextrin. Specifically, Bodor states "β-cyclodextrin has been of special interest because of its cavity size, but its relatively low aqueous solubility has limited its use in the pharmaceutical field." *See*, Col. 2, lines 7-10.

9. With respect to the solubility of anti-neoplastic agents with hydroxypropyl-beta-cyclodextrin, of the myriad of water-insoluble, anti-neoplastic compounds known in the art, Bodor only discloses nineteen contemplated compounds. *See*, Col. 15, lines 5-10. Further, Bodor only discloses working examples for solubilizing Methotexate, Chlorambucil, Lomustine and Melphalan in hydroxypropyl-beta-cyclodextrin. *See*, Col. 76, lines 44-49; Col. 77, Table III; Col. 76, line 65 – Col. 79, line 44 including Tables V – VIII.

   One of ordinary skill in the art reading the general disclosure of Bodor with the limited number of anti-neoplastic compounds disclosed would not combine that disclosures with the disclosure of Pardee to reach the present invention with a reasonable expectation of success. There are many water-insoluble, antineoplastic compounds (*e.g.* taxol (paclitaxel), etoposide, vincristine, vinblastine, cisplatin, staurosporin, UCN-01, *etc.*) that are not readily solubilized with beta-cyclodextrin or hydroxypropyl-beta-cyclodextrin. Specifically, taxol, an anti-neoplastic as disclosed in Pardee, is not rendered soluble in beta-cyclodextrin or hydroxypropyl-beta-cyclodextrin. Further, Bodor discloses that etoposide is a contemplated water-insoluble anti-neoplastic compound which can be solubilized with hydroxypropyl-beta-cyclodextrin. In fact, etoposide, a topoisomerase poison disclosed in Pardee, is not rendered soluble in beta-cyclodextrin or hydroxypropyl-beta-cyclodextrin as suggested by Bodor.

10. The ability of beta-cyclodextrin or hydroxypropyl-beta-cyclodextrin to solubilize water-insoluble or poorly water-soluble drugs/compounds depends on the ability of the drug/compound to fit into the cavity of the cyclodextrin ring system. Thus, factors such as size and charge can preclude the introduction of a drug/compound into the

cavity of beta-cyclodextrin or hydroxypropyl-beta-cyclodextrin due to steric hindrance contraints. As described, Bodor only discloses nineteen contemplated anti-neoplastic compounds that could be solublized in hydroxypropyl-beta-cyclodextrin. The chemical structures of some of the disclosed anti-neoplastic compounds are disclosed in Bodor. *See*, Col. 46 and 57-60. One of ordinary skill in the art reading Bodor would readily recognize that these disclosed chemical structures are much smaller in size when compared to the chemical structures of the β-lapachone or analogs or derivatives or taxol compounds disclosed in Pardee and that while the Bodor compounds may fit into the cavity of beta-cyclodextrin or hydroxypropyl-beta-cyclodextrin the larger compounds of Pardee would not readily fit into the cavity. Also, as discussed above, taxol is known not to be rendered soluble in beta-cyclodextrin or hydroxypropyl-beta-cyclodextrin with reasonable quantities and is not stable upon dilution with water or saline that are necessary for parenteral administration.

Since Bodor only generally discloses anti-neoplastic compounds which are contemplated to be solubilized by hydroxypropyl-beta-cyclodextrin and these contemplated compounds are much different in chemical structure (*i.e.* smaller in size, differing ring structures) from the chemical structure of β-lapachone or its analogs and derivatives and the chemical structures of many anti-neoplastic compounds, most notably taxol and etoposide, which as described are not readily soluble in beta-cyclodextrin or hydroxypropyl-beta-cyclodextrin, Bodor does not provide sufficient, specific guidance to one of ordinary skill in the art to select the specific parameters and choices necessary to reach the present invention. Therefore, one of ordinary skill in the art would have no reasonable expectation of success combining the teachings of Pardee and Bodor to reach the presently claimed invention.

11. The present invention discloses that combining, mixing, and/or complexing β-lapachone with hydroxypropyl-beta-cyclodextrin increases the aqueous solubility of β-lapachone, improves the stability of β-lapachone to photoreduction, and shows that the solubility of β-lapachone increases linearly with the increase in hydroxypropyl-beta-cyclodextrin concentration. *See*, specification at page 8, lines 8-12; Table 2;

page 9, lines 5-11; page 21, line 5 – page 23, line 7; page 24, line 6 – page 25, line 7; Figures 1-2. One of ordinary skill in the art would not have expected a pharmaceutical composition comprising β-lapachone solubilized by beta-cyclodextrin or hydroxypropyl-beta-cyclodextrin to be therapeutically effective. As described *supra*, Bodor only discloses nineteen anti-neoplastic/anti-tumor agents contemplated for parenteral formulation with hydroxypropyl-beta-cyclodextrin. *See*, Col. 15, lines 5-10. Moreover, Bodor only discloses working examples for the solubility of Methotexate, Chlorambucil, Lomustine and Melphalan in hydroxypropyl-beta-cyclodextrin. *See*, Col. 76, lines 44-49; Col. 77, Table III; Col. 76, line 65 – Col. 79, line 44 including Tables V – VIII. Specifically, in describing the solubility of these compounds Bodor discloses that when Chlorambucil, Lomustine and Melphalan are complexed with hydroxypropyl-beta-cyclodextrin to increase solubility, degradation of the drug occurred and in the case of Chlorambucil, significant degradation occurred. *See*, Col. 78, lines 30-49.

As the specification demonstrates, the present invention teaches that when β-lapachone is combined, mixed, or complexed with hydroxypropyl-beta-cyclodextrin, β-lapachone shows significantly better stability in the dark at 5 days and 21 days and also when exposed to normal room brightness at room temperature. *See*, page 24, line 6 – page 25, line 7. Specifically, this teaching is critical for producing a pharmaceutical composition comprising a therapeutically effective amount of β-lapachone since the administration and use of the pharmaceutical composition depends upon the ability of the drug of interest (*i.e.* β-lapachone or analogs and derivatives thereof) to be administered and delivered to a particular target (*i.e.* a cancer cell). To do so effectively, the drug of interest must be soluble and stable (not readily degradable) and remain soluble and stable prior to administration (*e.g.* parenteral). The results described in the specification demonstrate that the claimed invention displays the surprising, unexpected and superior stability of a pharmaceutical composition comprising a therapeutically effective amount of β-lapachone solubilized by beta-cyclodextrin or hydroxypropyl-beta-cyclodextrin. These results were not taught or suggested by either Pardee or Bodor alone or in combination. Therefore, the combination of Pardee and Bodor could not lead the ordinarily skilled artisan to the unexpected and superior advantages (increased

stability of β-lapachone) that the claimed invention provides.

12. It is my view that one of ordinary skill in the art would not be motivated to combine Pardee and Bodor nor would one of ordinary skill in the art have a reasonable expectation of success combining the teachings of Pardee and Bodor to reach the presently claimed invention. Further, the combination would not direct the artisan to the unexpected and superior stability of a pharmaceutical composition comprising a therapeutically effective amount of β-lapachone solubilized by beta-cyclodextrin or hydroxypropyl-beta-cyclodextrin. I am of the view that the present claimed pharmaceutical compositions are not obvious in view of the cited art.

13. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Dasharatha Reddy, Ph.D.
Signed this day 3 of June, 2004